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Relationship between race and outcome in Asian, Black, and Caucasian patients with spontaneous intracerebral hemorrhage: Data from the Virtual International Stroke Trials Archive and Efficacy of Nitric Oxide in Stroke trial

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Abstract

Background and purpose: Although poor prognosis after intracerebral hemorrhage relates to risk factors and hematoma characteristics, there is limited evidence for the effect of race–ethnicity.

Methods: Data from 1011 patients with intracerebral hemorrhage enrolled into hyperacute trials and randomized to control were obtained from the Virtual International Stroke Trials Archive and Efficacy of Nitric Oxide in Stroke Trial. Clinical characteristics and functional outcome were compared among three racial groups – Asians, Blacks, and Caucasians.

Results: The majority of patients were Caucasian (78.1%) followed by Asians (14.5%) and Blacks (5.5%). At baseline, Caucasians were older and had larger hematoma volumes; Blacks had lower Glasgow Coma Scale and higher systolic blood pressure (all $p < 0.05$). Although the primary outcome of modified Rankin Scale did not differ at 90 days ($p = 0.14$), there were significant differences in mortality ($p < 0.0001$) and quality of life (EQ-5D $p < 0.0001$; EQ-VAS $p = 0.015$). In test of multiple comparisons, Caucasians were more likely to die ($p = 0.0003$) and had worse quality of life (EQ-5D $p = 0.003$; EQ-VAS $p < 0.0001$) as compared to Asians.

Conclusion: Race–ethnicity appears to explain some of the variation in clinical characteristics and outcomes after acute intracerebral hemorrhage. Factors that explain this variation need to be identified.

Keywords

Intracerebral hemorrhage, ethnicity, race, outcome, randomized controlled trial, Virtual International Stroke Trials Archive, Efficacy of Nitric Oxide in Stroke

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Introduction

Spontaneous intracerebral hemorrhage (ICH) is a severe cause of stroke associated with significant morbidity and mortality.¹ In contrast to ischemic stroke where incidence has declined in recent decades, the

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number of admissions for ICH continues to increase.^{2,3} Variations in ICH incidence and outcome occur between different race-ethnicity groups. A higher incidence of ICH is observed among Black and Hispanic populations when compared with Caucasians.^{4–6} The SINO-MONICA-Beijing study reported greater mortality due to ICH in China compared to other countries.⁷ Death caused by stroke was reported to be higher in Asians compared to Caucasian patients in the UK and Canada.^{8,9} The causes for these observations are unclear and might be explained by increased prevalence of risk factors such as diabetes and hypertension among Asians.^{10–13} Additional explanatory factors also appear to include blood pressure (BP) at presentation.^{5,14–16} However, studies assessing ICH in different race-ethnicity groups have mostly involved small centers with limited numbers of patients and have restricted comparisons to differences between two racial populations.^{5,6,17,18}

In this study, we compared baseline clinical characteristics and functional outcome in three racial groups in patients with ICH. The data came from the Virtual International Stroke Trials Archive (VISTA) collaboration¹⁹ and the Efficacy of Nitric Oxide in Stroke (ENOS) trial.²⁰

Methods

Data sources

The included patients came from the VISTA-ICH archive, which includes data from a number of completed randomized controlled trials (RCTs)¹⁹ and the acute ENOS BP trial.^{20,21} Patients were those with spontaneous ICH, as diagnosed locally using routine neuroimaging, and who were treated within 6 h of onset. We included patients allocated to the control group in ENOS, as patients assigned to intervention are not included in VISTA. Patients were excluded if: age < 18, ICH attributed to trauma, planned surgical evacuation, previously dependent (modified Rankin Scale, mRS ≥ 2), concurrent illness with life expectancy < 6 months, pregnant or breast feeding women, and those already participating in a study involving another drug or device.

Baseline data

Data at baseline were obtained for age, sex, time from ictus to treatment, medical history (previous stroke, hypertension, ischemic heart disease, diabetes mellitus, hypercholesterolemia, atrial fibrillation, and prior antithrombotic use), level of consciousness (Glasgow Coma Scale, GCS), stroke severity (National Institutes of Health Stroke Scale, NIHSS), systolic

blood pressure (SBP), and heart rate. Race (and ethnicity) was defined as Asian (Filipino, Oriental, Asian, Indian, Palestinian, and Arabic), Black (Black, African/American, Caribbean), Caucasian (White or Caucasian), and Others (American Indian, mixed-colored, mixed, Hispanic, colored, Hawaiian and Pacific Islanders).

Outcome data

Outcome at day 90 was assessed using the mRS and all-cause mortality; where available, data on disability (Barthel Index, BI) and quality of life (European quality of Life-5 dimensions, EQ-5D) were also assessed.

Neuroimaging

Depending on trial protocol, CT scans were performed following treatment and then again at 72 h. Information from CT scans was collected for hemorrhage location, lesion volume, edema volume, presence of mass effect, subarachnoid bleeding, intraventricular hemorrhage, brain atrophy, and leukoaraiosis.

Statistical analysis

The primary outcome was the mRS at day 90. Baseline characteristics and outcomes were compared by Pearson χ^2 test for categorical variables and analysis of variance for continuous variables. The relationship between baseline hematoma volume and mRS between ethnic groups was analyzed using multiple regression. Individual comparisons between ethnic groups were made using Bonferroni correction. Mortality was assessed using Kaplan–Meier curves and Cox Regression. Analyses were adjusted for age, NIHSS, ICH volume, and time to treatment. Confidentiality agreements precluded identification of the individual trials in VISTA-ICH and so analyses were not adjusted for trial. Since death is present in outcome scores such as mRS (6), HUS (0), and BI (–5), death was scored for European quality of life-visual analogue scale (EQ-VAS) as –1. Statistical significance was set at $p \leq 0.05$. All analyses were performed using SPSS (version 21) running on an Apple Mac computer.

Results

Baseline clinical and neuroimaging characteristics

A total of 1011 patients were identified: 979 recruited from VISTA-ICH¹⁹ and 32 from ENOS.²⁰ The mean age was 66.2 years, 63.2% were male, the average time to treatment was 3.7 h and the mean GCS was 13.8 (Table 1). The majority of patients were Caucasian

Table 1. Baseline characteristics of 1011 patients with intracerebral hemorrhage by ethnicity

Demographics	n	All	Caucasian	Asian	Black	Other	2p	C vs. A 2p	C vs. B 2p	A vs. B 2p
Number of patients (%)		1011	790 (78.1)	147 (14.5)	56 (5.5)	18 (1.8)				
<i>Clinical findings</i>										
Age (years)	1011	66.2 (12.5)	67.7 (12.1)	61.3 (12.5)	58.4 (11.3)	61.9 (11.0)	<0.001	<0.0001	<0.0001	0.13
Sex, male (%)	982	621 (63.2)	489 (63.3)	40 (65.6)	32 (57.1)	10 (71.4)	0.56	0.64	0.39	0.33
OTT (hrs)	1007	3.7 (1.2)	3.7 (1.2)	3.6 (1.4)	3.4 (1.2)	3.7 (1.2)	0.08	0.26	0.035	<0.0001
<i>Medical history</i>										
Previous stroke (%)	1011	106 (10.5)	71 (9.0)	24 (16.3)	8 (14.3)	3 (16.7)	0.017	0.011	0.23	0.83
Hypertension (%)	1011	813 (80.4)	613 (77.6)	133 (90.5)	52 (92.9)	15 (83.3)	<0.0001	<0.0001	0.006	0.78
IHD (%)	1011	105 (10.4)	92 (11.6)	10 (6.8)	3 (5.4)	0 (0)	0.07	0.11	0.19	1.00
Diabetes mellitus (%)	1011	177 (17.5)	135 (17.1)	25 (17.0)	11 (19.6)	6 (33.3)	0.89	1.00	0.59	0.68
HC (%)	997	49 (4.8)	43 (5.4)	5 (3.4)	1 (1.8)	0 (0)	0.49	0.40	0.42	1.00
Atrial fibrillation (%)	1011	68 (6.7)	62 (7.8)	4 (2.7)	2 (3.6)	0 (0)	0.047	0.022	0.43	0.67
Antithrombotic(s) (%)	162	162 (16.0)	143 (18.1)	8 (5.4)	7 (12.5)	4 (22.2)	0.005	1.00	0.77	0.87
NIHSS (/42) ^a	1008	13.7 (1.9)	13.7 (5.6)	13.3 (6.0)	15.1 (7.4)	13.7 (1.9)	0.12	0.37	0.08	0.07
GCS (/15)	1010	13.8 (1.8)	13.8 (1.8)	13.4 (1.9)	13.2 (2.2)	14.1 (1.7)	0.010	0.037	0.015	0.37
Systolic BP (mmHg)	1008	174.4 (29.2)	173.1 (29.3)	176.7 (26.5)	185.7 (40.0)	174.4 (29.2)	0.005	0.18	0.002	0.041
Diastolic BP (mmHg)	1007	93.2 (19.0)	91.6 (18.5)	97.1 (18.5)	106.0 (21.1)	93.8 (20.8)	<0.001	0.001	<0.0001	0.003
Heart rate (bpm)	1005	80.0 (15.1)	78.1 (15.4)	76.6 (13.8)	79.9 (14.6)	78.2 (14.1)	0.34	0.27	0.40	0.14
<i>Neuroimaging</i>										
<i>Hematoma location (%)</i>										
Lobar	863	134 (13.3)	122 (15.4)	5 (3.4)	7 (12.5)	0	0.001	<0.0001	0.57	0.045

(continued)

Table 1. Continued

Demographics	n	All	Caucasian	Asian	Black	Other	2p	C vs. A 2p	C vs. B 2p	A vs. B 2p
Subcortical white matter	893	685 (67.8)	541 (68.5)	93 (63.3)	42 (75.0)	9 (50.0)	0.006	0.30	0.73	0.34
Thalamus	600	217 (21.5)	181 (22.9)	22 (15.0)	10 (17.9)	4 (22.2)	1.00	1.00	1.00	1.00
Brain stem/cerebellum	893	21 (2.1)	17 (2.2)	2 (1.4)	1 (1.8)	1 (5.6)	0.82	0.75	1.00	1.00
Hematoma volume (cm ³)	996	22.7 (23.1)	24.2 (24.9)	17.8 (13.1)	15.8 (14.1)	18.5 (17.3)	0.005	0.03	0.014	0.34
Edema volume (cm ³)	874	13.9 (15.7)	14.9 (16.9)	11.1 (9.2)	9.9 (10.4)	8.1 (7.8)	0.007	0.015	0.041	0.48
Midline shift (%)	885	623 (61.6)	488 (61.8)	90 (61.2)	38 (67.9)	7 (38.9)	0.62	0.67	0.43	0.71
SAH (%)	1007	80 (7.9)	73 (9.2)	3 (2.0)	1 (1.8)	3 (16.7)	0.003	0.02	0.05	1.00
IVH (%)	876	286 (28.3)	234 (29.6)	33 (22.4)	17 (30.4)	2 (11.1)	0.22	0.14	0.75	0.26
Hydrocephalus (%)	860	619 (61.2)	517 (65.4)	64 (43.5)	29 (51.8)	9 (50.0)	<0.001	<0.0001	0.004	0.74
Leukoaraiosis (%)	619	287 (28.4)	251 (31.8)	21 (14.3)	12 (21.4)	3 (21.4)	0.28	0.29	0.18	0.66
Cerebral atrophy (%)	1007	552 (54.6)	469 (59.4)	50 (34.0)	21 (37.5)	12 (66.7)	<0.001	<0.0001	0.002	0.74

BP: blood pressure; GCS: Glasgow Coma Scale; HC: hypercholesterolemia; IHD: ischemic heart disease; IVH: intraventricular hemorrhage; OTT: onset to treatment; SAH: subarachnoid hemorrhage. Data are number (%) or mean (standard deviation). Comparisons by chi-square test or one-way analysis of variance.

^aCalculated²² from Scandinavian Stroke Scale in ENOS.

Table 2. Clinical and radiological outcomes by race groups

	n	All	Caucasian	Asian	Black	Other	2p	C vs. A 2p	C vs. B 2p	A vs. B 2p
Patients		1011	790	147	56	18				
<i>Clinical</i>										
mRS (/6)										
Day 7	538	4.1 (1.1)	4.2 (1.1)	4.2 (0.8)	3.9 (1.3)	4.6 (0.5)	0.36	1.00	0.07	0.12
Day 90	873	3.2 (1.6)	3.2 (1.6)	3.0 (1.6)	3.4 (1.7)	3.1 (1.8)	0.14	0.18	1.00	0.37
NIHSS (/42) ^a										
Day 1	936	13.1 (7.0)	13.1 (7.0)	12.8 (6.7)	13.2 (8.1)	12.4 (6.5)	0.89	1.00	1.00	1.00
Day 3	564	12.5 (8.0)	12.7 (8.2)	11.0 (6.3)	11.6 (8.3)	14.8 (7.0)	0.29	0.42	1.00	1.00
Day 7	534	10.8 (7.1)	10.9 (7.9)	10.2 (6.1)	10.7 (7.5)	13.1 (6.7)	0.80	1.00	1.00	1.00
Day 90	958	8.1 (9.8)	8.1 (10.1)	6.0 (5.7)	9.6 (10.4)	9.7 (10.6)	0.31	0.88	0.96	0.41
Barthel Index (/100)										
Day 7	539	28.9 (31.1)	28.6 (31.2)	30.6 (29.1)	33.9 (36.5)	14.4 (16.1)	0.010	1.00	1.00	1.00
Day 90	872	63.0 (37.4)	62.9 (37.6)	66.0 (35.7)	56.4 (39.0)	66.5 (39.1)	0.28	1.00	0.68	0.34
Day 90										
Death (%)	1011	211 (20.9)	189 (23.3)	11 (7.5)	9 (16.1)	2 (11.1)	<0.001	<0.001	0.59	0.33
EQ-5D (/1)	487	0.29 (0.37)	0.25 (0.36)	0.46 (0.40)	0.31 (0.40)	0.40 (0.39)	<0.001	<0.001	1.00	0.18
EQ-VAS (/100)	321	46.0 (33.5)	43.3 (33.6)	57.0 (30.2)	44.2 (35.2)	42.5 (60.1)	0.015	0.012	1.00	0.34
Neuroimaging										
ICH vol. (cm ³)										
Follow-up scan	523	32.3 (32.2)	34.7 (34.4)	26.2 (23.8)	23.7 (23.6)	18.9 (24.1)	0.017	0.07	0.14	1.00
72 h	930	27.3 (28.6)	28.7 (30.4)	23.3 (19.7)	20.1 (20.3)	21.6 (20.4)	0.019	0.13	0.09	1.00

(continued)

Table 2. Continued

	n	All	Caucasian	Asian	Black	Other	2p	C vs. A 2p	C vs. B 2p	A vs. B 2p
Edema vol. (cm ³)										
Follow-up scan	428	31.8 (31.8)	34.1 (33.9)	29.1 (25.7)	19.7 (20.8)	19.7 (18.4)	0.030	0.65	0.038	0.46
72 h	924	33.6 (30.9)	33.6 (30.9)	29.9 (22.1)	22.0 (19.6)	24.8 (23.4)	0.009	0.53	0.012	0.26
IVH (%)										
Follow-up scan	399	195 (19.3)	145 (18.4)	35 (23.8)	14 (25.0)	1 (5.6)	0.98	0.90	1.00	1.00
72 h	811	344 (34.0)	277 (35.1)	46 (31.3)	19 (33.9)	2 (11.1)	0.41	0.54	0.55	1.00
72 h										
SAH (%)	566	97 (9.6)	87 (11.0)	7 (4.8)	2 (3.6)	1 (5.6)	0.23	0.21	0.20	0.71
Hydrocephalus (%)	791	605 (59.8)	498 (63.0)	67 (45.6)	31 (55.4)	9 (50.0)	<0.001	<0.001	0.016	0.60
Midline shift (%)	790	628 (62.1)	490 (62.0)	94 (63.9)	37 (66.1)	7 (38.9)	0.54	0.25	0.72	0.37

A: Asians; B: Blacks; C: Caucasians; EQ-5d: European Quality of Life-5 dimensions; EQ-VAS: European Quality of Life-Visual Analogue Scale; ICH: intracerebral hemorrhage; IVH: intraventricular hemorrhage; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; SAH: subarachnoid hemorrhage. Data are number (%) and mean (standard deviation). Comparisons between group differences made by chi-square test or analysis of variance; multiple comparisons include Bonferroni correction.

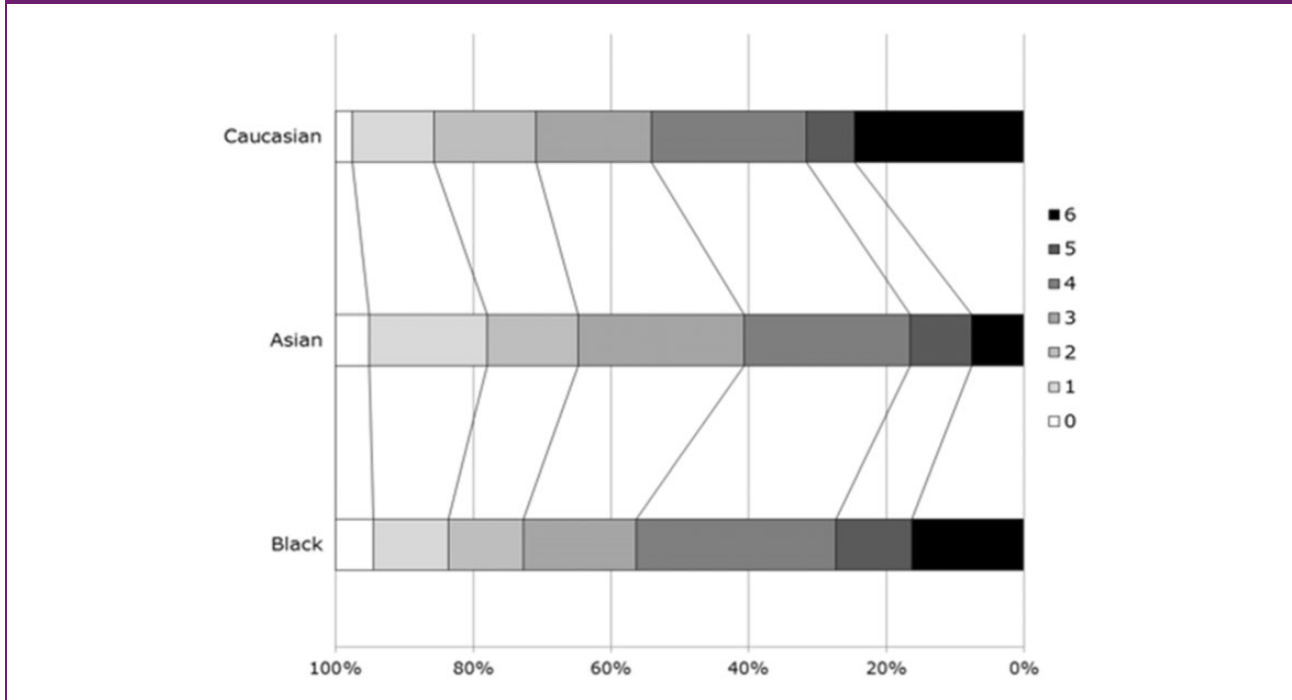
^aCalculated from Scandinavian Stroke Scale in the ENOS trial.²²

Range of scores for patients in ENOS:

Barthel Index: -5 (death) to 0 (severe disability) to 100 (no disability).

Health utility status (HUS, derived from European Quality of Life-5 dimensions, EQ-5d): -0.5 (very poor quality of life, 0 (death) to 1.0 (perfect quality of life). European Quality of Life-Visual Analogue Scale (EQ-VAS): -1 (death), 0 (very poor) to 100 (excellent).

Zung Depression Scale (ZDS): 0 (normal), 100 (severe depression) to 102.5 (death).

Figure 1. Distribution of modified Rankin scores between the three race groups at day 90.

(78.1%), followed by Asians (14.5%) and Blacks (5.5%). Less than 2% were in the 'other group' and these were removed from further analyses. When analyzed by baseline characteristics, Black patients were younger and more likely to have a previous history of hypertension and higher SBP at baseline. Caucasian patients trended to have more atrial fibrillation, and Asian patients were less likely to have a prior history of antithrombotic use. The mean ICH volume was 22.7 cm³ and most hematomas were located in the deep subcortical white matter of the brain (Table 1).

Clinical outcomes

Table 2 shows clinical and radiological outcome measures by ethnicity. The primary outcome, mRS, did not differ between race groups at either day 7 or 90 (Figure 1). Similarly, there was no difference in NIHSS during the first seven days. Whilst the BI differed at day 7, it was not significant at day 90 using a test of multiple comparisons. Quality of life, assessed using two measures (health utility status derived from EQ-5D and EQ-VAS), differed between the three groups (Table 2, Figure 2); following adjustment for multiple comparisons, Caucasians had a worse quality of life scores for both EQ-5D and EQ-VAS as compared to Asians (Table 2). Adjusted survival rates differed between race-ethnicity groups (Table 2, Figure 3), explained by a significant difference between Asians

and Caucasians ($p = 0.005$). There were no other significant differences for other outcomes.

Neuroimaging outcomes

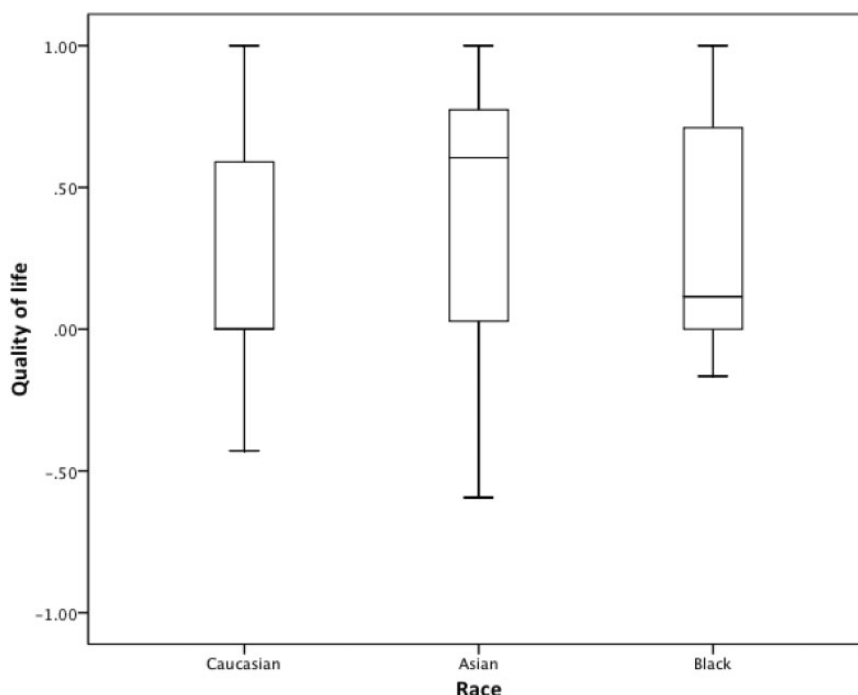
ICH volume differed across the race groups on both the first follow-up scan (Table 2, Figure 4) and at 72 h. (Table 2); in both cases, Caucasians tended to having large hematoma (Table 2). Similarly, edema volumes differed across the race groups on both the first follow-up scan and at day 7 with Caucasian patients have large edema volumes than Black patients. The presence of hydrocephalus also differed and was highest in Caucasians. The presence of intraventricular hemorrhage, subarachnoid hemorrhage and midline shift did not differ between the race groups (Table 2).

When assessing the relationship between baseline hematoma volume and mRS, there was a significant difference in the slope of the regression lines between the race-ethnicity groups; Blacks and Asians appeared to have a worse mRS for a given hematoma volume ($p = 0.047$; online Supplementary Figure 1). There were no other significant differences between any of the other comparison groups.

Discussion

To our knowledge, this is the first study to examine clinical and neuroimaging features and outcomes in

Figure 2. Box plots of European Quality of Life-5 dimension-3 level scores at day 90. Comparison by ANOVA $2p < 0.001$; Caucasian vs. Asian $2p < 0.001$, Caucasian vs. Black 1.00 , Asian vs. Black $2p = 0.18$.



ICH patients across three race groups. Significant differences in age, the frequency or previous stroke and hypertension, GCS, BP, and ICH volume were present between Caucasian, Asian, and Black patients. Similarly, differences in neuroimaging features were present for hematoma location and volume, edema volume, and the presence of subarachnoid hemorrhage, hydrocephalus, leukoaraiosis, and cerebral atrophy. Although there was no difference in the primary outcome of mRS at day 90, significant differences in case fatality and quality of life were present. Similarly, differences in ICH and edema volume, and the presence of hydrocephalus, were present between the race groups.

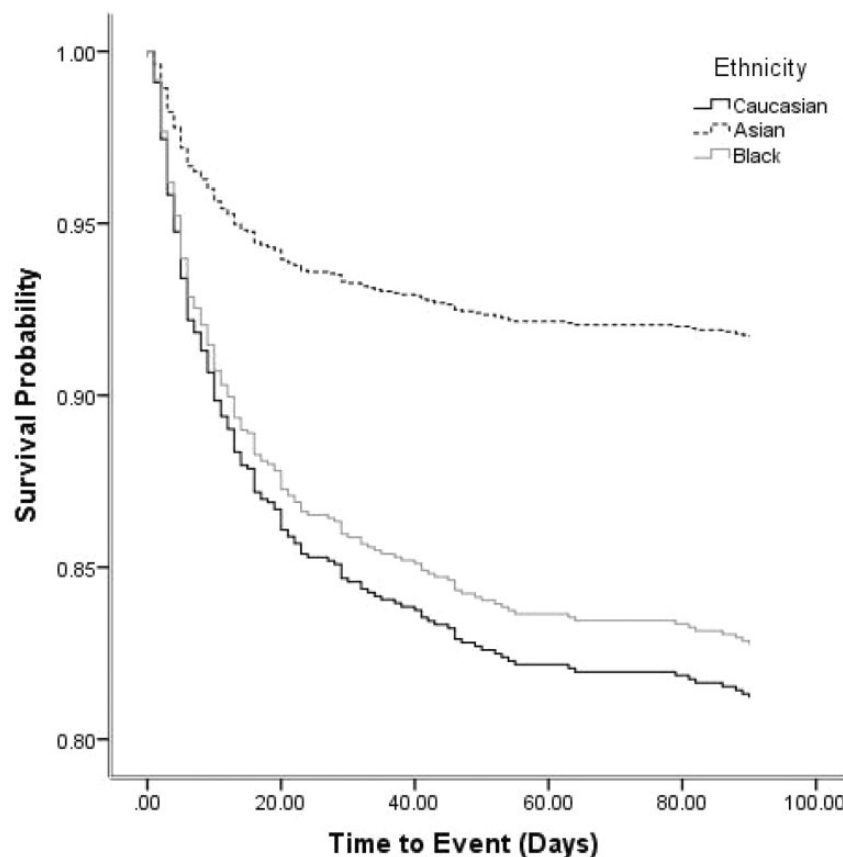
Black patients were younger and a larger proportion had a history of hypertension which could be associated with increased smoking, alcohol, and drug abuse.^{17,18} It is noteworthy that BP in Blacks was higher on admission and probably reflects inadequate control, poor compliance with treatment or treatment resistance.^{17,23} Higher BP in the acute phase of ICH is common²⁴ and associated with neurological deterioration through hematoma expansion and re-bleeding.^{24–26} The treatment implications of racial difference in BP lowering need investigation as evidence suggests that early treatment is both safe and feasible^{20,27} and is now recommended in guidelines.^{28,29} In contrast to a previous report of greater mortality in Blacks for every stroke

subtype,³⁰ VISTA-ENOS found reduced survival in Caucasians with ICH. This finding is difficult to explain and may relate to hemorrhage location, inherent susceptibility to ICH or quality of care or simply that race-ethnic differences persist even after controlling for such characteristics.

As would be expected, ICH survivors had a quality of life worse than that reported in the general population.^{31,32} The difference between Caucasians and Asians has been reported previously^{14,33} and may relate to family values, cultural attitudes, and care preferences.^{33,34} In one study, Asians were more likely to be living at home, whilst Caucasians were less likely to be discharged home despite better functional improvement.³⁵ Apart from cultural and family factors, age, female sex, stroke severity, persistent neglect, and socioeconomic status have also been shown to affect quality of life after stroke.^{36,37}

The strengths of the study include a relatively large sample size for a study population with detailed clinical, radiological information, and multiple functional endpoints. The included patients were from neutral RCTs or control group and therefore assessment of the race-ethnic differences avoided the confounding effects of active treatment. However, there are some limitations. First, the analysis on observational data from RCTs has the disadvantage that patients were

Figure 3. Cox regression with adjustment for age, baseline systolic blood pressure, stroke severity (NIHSS), hematoma volume, and time to treatment: overall $p = 0.021$; Asians vs. Caucasians, hazard ratio 0.42 (95% CI 0.22, 0.77); $p = 0.005$.

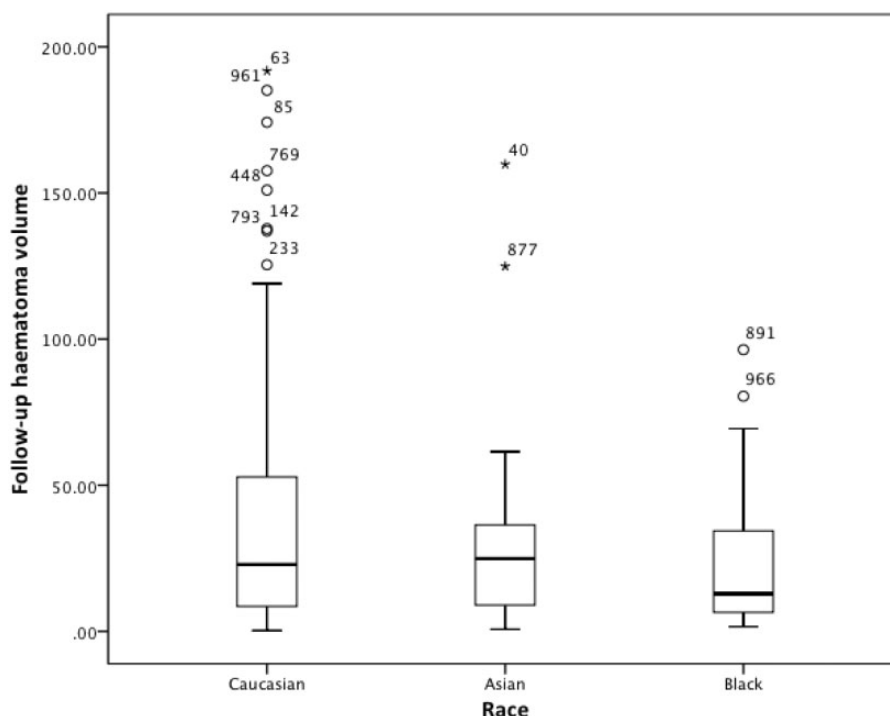


included on the basis of pre-specified selection criteria. It is possible that those with more severe stroke with reduced level of consciousness, older patients with multiple comorbidities and pre-existing do not resuscitate orders, may have been excluded. Therefore, the results may not be applicable to a population of unselected ICH patients. Second, the VISTA collaboration does not reveal the identities of the individual trials and so it is uncertain as to what inclusion criteria were used to select patients. Additionally, analyses could not be adjusted for the source trials, which is important since trials themselves are a determinant of outcome. Nevertheless, the data were subject to strict verification and so the results are externally valid. Third, ethnicity relates to culture, geography, language and it is not clear from the data if this was self-reported or defined by the investigator. Fourth, to compensate for limited numbers, distinct subpopulations were grouped into one ethnic group (for example Asians included people from China, Philippines, the Indian subcontinent, and Arabian peninsula), whilst small groups present in the 'others' category were excluded. This may have not been appropriate as stroke risk and

functional outcome vary within subpopulations living in the same country and between countries.^{38,39} Last, the analysis is limited to trials sharing information within the collaboration and therefore those studies that are not represented in VISTA would not have been included.

In conclusion, this analysis from hyperacute trials in hemorrhagic stroke found significant race differences in baseline clinical characteristics and hematoma measures. There were no difference in the primary outcome of death or dependency but differences in death rates and quality of life were apparent. Further studies are needed to which factors explain race-ethnic differences and whether these differences become larger over time. Our results suggest that future trials should undertake measures to ensure adequate representation of all major race-ethnic groups. This might include standard definitions for race-ethnicity that reflect common features but not limited to biological, cultural, and social differences. Further research is also needed to understand where inadequacies in health care systems exist and what interventions can be made to reduce such disparities. This could include allowing more resources to

Figure 4. Intracerebral hematoma volume on first follow-up imaging by race. Comparison by ANOVA $2p = 0.017$; Caucasian vs. Asian $2p = 0.07$, Caucasian vs. Black 0.14 , Asian vs. Black $2p = 1.0$.



developing countries or those without access to specialist stroke care teams.

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The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: VISTA is a non-profit collaboration of academics and commercial organizations. Each VISTA steering committee member has contributed to organization of clinical trials and where industry support was involved have acknowledged this in the individual trial publications. Philip M Bath is Stroke Association Professor of Stroke Medicine, Chief Investigator of ENOS, and an NIHR Senior Investigator. Joanna M Wardlaw was the neuroimaging lead of ENOS. No author involved in this work has any additional interest to report.

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